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Secondary metabolites with antitumor activity: a review

Metabólitos secundários com atividade antitumoral: uma revisão

Metabolitos secundarios con actividad antitumoral: una reseña

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Abstract
Cancer is a disease that presents as its main characteristic the uncontrolled growth of cells, which is currently numerous people annually. The available treatments such as chemotherapy cause many adverse effects in cancer patients because it also reaches the viable cells of the body. Plants have a wide variety of pharmacologically active compounds and are major sources for the development of new drugs with oncological potential. Biodiversity has been prospected in recent decades to discover and develop new drugs that are safer and more effective in the battle against cancer, acting more selectively with fewer toxic effects. Some drugs currently used in cancer treatment are derived from plants. Therefore, the present review aimed to address the general aspects of cancer and the pharmacological potential of secondary metabolites in cancer treatment. Through the bibliographic survey, it is concluded that there is much to be explored and plants present numerous therapeutic possibilities.
Keywords: Biodiversity; Cancer; Active compounds; Medicinal plants; Structural variety.

Resumo
O câncer, uma doença que apresenta como principal característica o crescimento descontrolado das células, essa acomete inúmeras pessoas anualmente. Os tratamentos disponíveis como a quimioterapia causam muitos efeitos adversos em pacientes oncológicos, devido ao fato de atingir também as células viáveis do organismo. As plantas dispõem de uma grande variedade de compostos ativos farmacologicamente e são grandes fontes para o desenvolvimento de novos fármacos com potencial oncológico. A biodiversidade vem sendo bioprospectada nas últimas décadas com a finalidade de descobrir e desenvolver novos fármacos mais seguros e efetivos na batalha contra o câncer, atuando de maneira mais seletiva com menos efeitos tóxicos. Alguns fármacos utilizados atualmente no tratamento do câncer são derivados de plantas. Portanto, a presente revisão objetivou abordar os aspectos gerais do câncer e o potencial farmacológico dos metabólitos secundários no tratamento oncológico. Através do levantamento bibliográfico, conclui-se que há muito que ser explorado e as plantas apresentam inúmeras possibilidades terapêuticas.
Palavras-chave: Biodiversidade; Câncer; Compostos ativos; Plantas medicinais; Variedade estrutural.

Resumen
Cáncer, una enfermedad que presenta como principal característica el crecimiento descontrolado de células, que actualmente es de numerosas personas anualmente. Los tratamientos disponibles como la quimioterapia causan muchos efectos adversos en pacientes con cáncer, debido al hecho de que también llega a las células viables del cuerpo. Las plantas tienen una amplia variedad de compuestos farmacológicamente activos y son fuentes importantes para el desarrollo de nuevos fármacos con potencial oncológico. La biodiversidad ha sido bioprospeccionada en las últimas décadas con el fin de descubrir y desarrollar nuevos fármacos que sean más seguros y eficaces en la lucha contra el

cáncer, actuando de forma más selectiva con menos efectos tóxicos. Algunos medicamentos que se usan actualmente en el tratamiento del cáncer se derivan de las plantas. Por lo tanto, la presente revisión tuvo como objetivo abordar los aspectos generales del cáncer y el potencial farmacológico de los metabolitos secundarios en el tratamiento del cáncer. A través de la encuesta bibliográfica, se concluye que hay mucho por explorar y las plantas presentan numerosas posibilidades terapéuticas.
Palabras clave: Biodiversidad; Cáncer; Compuestos activos; Plantas medicinales; Variedad estructural.

1. Introduction

Due to the stigma of mortality and pain, carcinoma is one of the diseases that causes the most panic in society, having a high worldwide prevalence rate. (Safarzadeh et al., 2014). The main anticancer treatments are still limited to chemotherapy, surgery, and radiotherapy, but there are many cases that do not respond to these protocols, showing the need for more efficient therapeutic methods (Costa-Lotufo et al., 2010).

According to the INCA estimate, by 2030, there will be 27 million new cases of cancer, 17 million deaths related to the disease, and 75 million of the population living with the disease. In Brazil, this disease represents the second leading cause of death among the population, second only to heart and circulatory system diseases (INCA, 2018).

The use of extracts and active principles found in medicinal plants are linked to the history of mankind. In recent years the interest in taking advantage of the pharmacological potential of plants is growing, as they are sources of active compounds that can be used in therapy (Brandão et al., 2010; Zardeto-Sabec et al., 2019).

The large number of medicines derived from natural products emphasizes the importance of these products that hold a wide structural variety of metabolites (Souza et al., 2007; Brandão et al., 2010). . Several reports have been published about the chemical potential of products of plant origin, in these data, it is observed that about 50% of the drugs used in the clinic for the treatment of neoplasms come from natural products or their semisynthetic derivatives (INCA, 2020). However, it is noted that all this potential is little explored since there are an estimated 250 to 350.000 species of plants cataloged on the planet, and only about 15% were made chemical and 6% biological investigations (Brandão et al., 2010).

Given the vast abundance of natural products and the great possibilities of finding therapeutic products, studies, in order to discover new compounds that have natural products as sources are great means to fight, cancer (Souza et al., 2007; Costa-Lotufo et al., 2010; Trindade et al., 2021).

2. Materials and Methods

A literature review on the subject of secondary metabolites with antitumor potential was conducted through electronic research using the Google Academic databases®, SCIELO (Scientific Electronic Library Online) and the Website of the National Cancer Institute (INCA). The inclusion criteria of the samples were the approach of the theme in question, as there are full texts available online in Portuguese and English. As this is a literature review, no evaluation of the scientific quality of the articles found was performed.

3. Development

3.1 Cancer

Having Larkin's Greek origin, the word cancer was first used by the father of medicine, Hippocrates (INCA, 2018). This word, cancer, is used to describe more than 100 malignant diseases that present as their main characteristic the uncontrolled and disorderly multiplication of cells, causing or not the possibility of invading tissues and organs (INCA, 2020).

The development of cancer occurs through the process called carcinogenesis or oncogenesis is based on the proliferation of abnormal cells, due to mutations in genes responsible for regulating the processes of cell growth and death, therefore triggering

an imbalance that causes the accumulation of abnormal cells. Thus, cancer can be defined as a disease resulting from genetic modifications caused by exposure to endogenous and exogenous carcinogens (Lee et al., 2016).

The multiplication of cancer cells can be controlled or not, being characterized as controlled when cell growth is localized and self-limited, expressing small changes in their shape and function, these cells can revert when the stimulus that causes the changes is removed. On the other hand, uncontrolled growth exhibits an abnormal mass of tissue that even before the end of the stimulus it continues to develop autonomously (INCA, 2011).

With regard to cancer treatments, the main approaches are limited to chemotherapy, surgery, radiotherapy, and immunotherapy. The use of post-surgical protocols that associate the use of chemotherapy, radiotherapy and monoclonal antibodies provided positive results in the treatment of some types of cancers, on the other hand, many tumors do not respond positively to the treatment imposed (Costa-Lotufo et al., 2010). However, treatments such as chemotherapy and radiotherapy produce several adverse effects, and organ and tissue toxicity are common (Dy & Adjei., 2013).

3.2 Chemoprevention

Chemoprevention comprises the chronic administration of drugs with the objective of preventing cell multiplication and disease evolution (Penny & Wallace, 2015). Chemotherapy used in combination or alone acts in the process of growth and multiplication of tumor cells (Gabriel et al., 2017). However, the major problem of the administration of these drugs in cancer treatment is the fact that drugs do not have specificity, so every cell type that has a high proliferative rate will also be affected (Iuchno & Carvalho, 2019).

Several drugs used in chemotherapy were isolated from plants including the alkaloid vinblastine indicated for the treatment of breast cancer, leukemia, lymphoma, lung cancer, and testicles. Another substance with antitumor potential and also alkaloid is the vincristine used in the treatment of leukemia. Taxol isolated from the plant *Taxus brevifolia* is used in the treatment of ovarian, breast, and lung cancer. The use of some plants may be associated with chemotherapy in order to reduce side effects, such as the use of rosemary to relieve malaise after chemotherapy sessions (Zardeto-Sabec et al., 2019).

3.3 Immunotherapy

The treatment of cancer through immunotherapy consists of the stimulation and recovery of the immune system, with the purpose of potentiating the immunological response against tumors, through the incitement of the tumors or providing immunological agents (Kakimi et al., 2017). The first studies on immunotherapy began in the 20th century, achieving a great advance in the 1980s, through the recognition of cellular receptors related to defense stimuli, especially in cancer cells (Kohrt et al., 2016). In a direct way, the immune system is affected when cancer is present, due to the fact that it cannot fight cancer cells efficiently and also because it is affected by antineoplastic treatments that do not only affect cancer cells (Freire, 2019).

There are two ways to obtain the immune response, which are passive and active. The passive pathway uses immunological agents such as antibodies or lymphocytes that are introduced into the patient, on the other hand, there is the active pathway that consists of stimulation of immune response through nonspecific immunological substances or agents such as cytokines (Kakimi et al., 2017).

Phytotherapy can also be combined with immunotherapy, most herbal and herbal complexes have the property of stimulating innate immunity that has a rapid response and has physical, chemical, and biological barriers with specialized cells (Medzhitov & Janeway., 2000; Safarzadeh et al., 2014).

3.4 Secondary metabolites: classification and mechanisms of action

The diversity of plant species results in large quantities and varieties of secondary metabolites, which are vital components for the development process of new medicines (Guo, 2017). Secondary metabolites are waste products of primary metabolism and are produced to act as chemical defense of the plant. They are classified as aromatic compounds, glycosides, flavonoids, alkaloids and terpenoids (Reyes-Silva, et al., 2020).

The differentiation between primary and secondary metabolism lies in the fact that secondary metabolites are not part of the processes that generate energy for the plant. The composition of metabolites is different in each plant, the production of different compounds suffers interference from abiotic and biotic factors, however, these products are vital for plants, functioning as attractive, repellent, herbivory deterrents, protection against UV radiation and pollution, intraspecific signaling and allelopathy (Borges & Amorim, 2020).

In the 20th century, there was a great advance in the research of natural products in the field of oncology, providing the discovery of substances that are currently used in cancer treatment (Costa-Lotufo et al., 2010). Discoveries such as the vinblastine and vincristine alkaloids found in *Catharanthus roseus* (L.) G. Don served as an incentive for research in this area (Brandão et al., 2010). These alkaloids and their semisynthetic sources are responsible for blocking mitosis still in its stage of metaphase and as a consequence of inducing cellular apoptosis (Sousa et al., 2019).

Natural products have contributed and are still contributors to the exploration and development of various drugs, enabling the cure of the many diseases that affect humanity (Cragg et al., 2012). It is estimated that only 5 to 15% of the plants have been investigated chemically and pharmacologically, so many plants containing medicinal values have not yet been studied (Krause & Tobin, 2013). The production of essential substances for plant survival, caused by problems they suffer in the environment, provides a variety of bioactive compounds that are mostly of high complexity (Souza, 2007).

Studies that seek new compounds that have antineoplastic activity and are derived from natural products are presenting themselves as an important tool for combating cancer, which is one of the major concerns of the modern era (Souza, 2007). About 60% of the drugs used in anticancer therapy originate in natural products such as vinyl alkaloids, taxanes, pedophile toxins (Costa-Lotufo et al., 2010; Safarzadeh et al., 2014). Plant-derived drugs can act through various mechanisms, such as causing disorder in the cell signal transduction pathways, cell cycle alteration, interference in the microtubules and inhibition of topoisomerase (Safarzadeh et al., 2014).

Camptothecin alkaloid extracted from *Camptotheca acuminata* acts by inhibiting topoisomerase an enzyme responsible for promoting the breaking of one of the DNA tapes (Brandão et al., 2010). The alkaloids of the vinca present activity directly in the microtubules and proteins, preventing the alignment of the child chromosomes and as a consequence interrupting mitosis, following to the cellular apoptosis, that is, interfering in the cell cycle (Almeida et al., 2005; Brandão et al., 2010; Safarzadeh et al., 2014).

Disorders in signal transduction pathways caused by herbal medicines generate the blockade of the main biochemical pathways: ap-1 and NF-KB activation routes, PTK-related signal transduction pathways, MAPK signaling pathway and Cox-2 signaling pathway (Safarzadeh et al., 2014). Natural sources are available in abundance and offer great opportunities to find compounds of great pharmaceutical interest, mainly to work in cancer treatments (Costa-Lotufo et al., 2010). Thus, new studies in the search for compounds as a source of natural products with antineoplastic activity are relevant as a method in coping with this disease (Souza, 2007).

3.5 Prototype molecules

With the onset of chemotherapy, many drugs were being discovered, studied and tested. From the beginning, humanity seeks the treatment of diseases through natural sources, thus bringing traditions and beliefs. For this reason, over the years, many of scientists and scholars have been improving their knowledge in this diverse area, obtaining proven evidence. Several molecules, of natural product origin, are sources of several prototype structures for the synthesis of new drugs, having advantages in the generation of drugs with fewer side effects as well as in the possibility of using them in their natural form (Oliveira, 2020).

For centuries, secondary metabolites have been studied in their numerous functions, from the production of food for humans to additives in animal feed. Plants produce these metabolites for their maintenance, because of both environmental stress, water scarcity, and high temperatures (López Palacios & Pena Valdivia, 2020).

Secondary metabolites are composed of several classes of compounds such as phenolics, alkaloids, saponins, terpenes, among others, and these, other subdivisions being the phenolic ones being the largest group (Hussein & El-Anssary, 2018). According to Vidal et al., (2019), secondary metabolites are identified through various analytical analyses and their use can be through the use of fresh plants, or through their pharmaceutical transformations. Among the phenolic class flavonoids is one of the groups of greatest representativeness and importance, being widely distributed in the plant kingdom, this group of metabolites has its biosynthesis performed from the phenylpropanoid pathway (Machado, 2008), presenting proven action being antioxidant, antibacterial, anti-inflammatory and anticancer (Ojeda, 2021). Table 1 shows the flavonoid structures of the main classes already observed.

Table 1. Chemical structure of some flavonoids of natural occurrence in plants.

Structural formula	Flavonoids	Replacements				
		5	6	7	3'	4'
Flavanin	Eriodictiol	OH	H	OH	OH	OH
	Hesperitin	OH	H	OH	OH	OMe
	Naringenin	OH	H	OH	H	OH
Flavanin	Catechina	OH	H	OH	OH	OH
	Gallocatechina	OH	H	OH	OH	OH
Flavone	Apigenin	OH	H	OH	H	OH
	Chrysin	H	H	OH	H	H
	Leteoine	OH	H	OH	OH	OH
Flavanol	Kamferol	OH	H	OH	OH	OH
	Myricetin	OH	H	OH	OH	OH
	Quercetin	OH	H	OH	OH	OH
Flavononol	Taxifolina	OH	H	OH	OH	OH
Isoflavone	Daidazine	H	H	OH	H	OH
	Genistein	OH	H	OH	H	OH
	Glycerin	OH	OMe	OH	H	OH
	Formononetin	H	H	OH	H	OMe

Source: Machado (2008).

Researchers in the area are looking for antineoplastic drugs that have easy administration and have minimal side effects. Recently, many drugs were discovered and studied obtaining specific activities such as metabolic mechanisms against tumor cell activity, inhibition of tumor neovascularization inducing cell death (Costa-Lotufo et al, 2010).

These studies provided the revelation of drugs that play an important role in the treatment of established neoplasms. Among these are chemotherapy patients such as vincristine and vinblastine, that were isolated from the vinca (*Catharanthus roseus*); the derivatives of podofilotoxin, obtained from rhizomes of *Podophyllum peltatum* L., *P. hexandrum* Royle; those from camptothecin, obtained from *Campotheca acuminata* Decne; the Taxol and Docetaxel extracted from *Taxus brevifolia* Nutt. and *T. baccata* L. (Vieira, 2020).

Another result they obtained from the studies was one of the most important and relevant: the discovery of Paclitaxel. This drug was initially extracted from the bark of *Taxus brevifolia* Nutt., an endemic Pacific's tree, this molecule has several asymmetric centers, proving effective against breast and ovarian tumors, and used in nanomolar concentrations. However, the extraction of the metabolite depends on the maturity of the plant and a large amount of the barks, and to solve this problem, the pharmaceutical industry uses semi-synthesis through the molecule 10-deacetylbacatin-III extracted from *Taxus baccata*, which presents the basic skeleton and features of Paclitaxel, this technique has the advantage of not using so many trees being a renewable source (Zhu et al, 2015). This drug was considered a milestone in the history of cancer treatment, as it is capable of providing selective death of cancer cells not harming normal cells, because it presents metallic checkpoints (Aal, 2021).

3.6 Substances with antitumor potential and their in vitro and in vivo *tests*

Several studies report the use of plants, marine organisms, and microorganisms in the treatment of diseases however, it is estimated that less than 2% of natural sources have already been explored for the purpose of detecting their constituents with antineoplastic activity, in addition, the understanding of new therapeutic targets in the treatment of the disease increases the probabilities of the discovery of new prototypes with anticancer potential (Costa-Lotufo et al, 2010).

Plant extracts and molecules, in general, which present antitumor activity should induce interruption of the cell cycle and/ or death by apoptosis of tumor cells, and for these prototype molecules to become drugs, validations of their activities are necessary through in vitro and/or in vivo tests, in order to prove their effectiveness (Pompilho & Miguel, 2013). The information obtained in the bibliographic research about substances of plant origin that have antineoplastic activity was organized in a table.

Table 2. The relationship between metabolites and they are respective in vivo and in vitro tests.

Origin	Active metabolite	in vivo	in vitro	References
Capraria biflora L. (Schrophulariaceae)	Biflorin	Potent cytotoxic activity	Potent cytotoxic activity	(Costa-Lotufo et al, 2010)
Pisolithustinctorius (fungus)	Pisosterol	Studies with Sarcoma 180 have shown that it also inhibits tumor growth	Has cytotoxic activity in tumor cells	(Costa-Lotufo et al, 2010)
Sorangium cellulosum (bacteria)	Ixabepilone* (Analogous to Epotilona B)	Potent antitumor activity	Potent antitumor activity	(Barreiroe & Bolzani, 2009)
Salvia prionitis Hance (Labiatae)	Salvicin	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)

Tabebuia avellanedae Lorentz ex Griseb (Bignoniaceae)	β-lapachona	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Catharanthus roseus (L.) G. Don. (Apocynaceae)	Vinblastine	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Catharanthus roseus (L.) G. Don. (Apocynaceae)	Vincristine	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Catharanthus roseus (L.) G. Don. (Apocynaceae)	Vinorelbine* (nor-5'-anhydrovimblastin) derived from Vimblastin	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Catharanthus roseus (L.) G. Don. (Apocynaceae)	Vindesine* (4-desacetyl vimblastin sulfate) derived from Vimblastin	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Camptotheca acuminata Decne. (Cornaceae)	Camptothecin	Potent antitumor activity	Insufficient antitumor activity	(Brandão et al., 2010)
Camptotheca acuminata Decne. (Cornaceae)	Irinotecan (derived from Camptothecin)	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Camptotheca acuminata Decne. (Cornaceae)	Topotecan (derived from Camptothecin)	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Podophyllum peltatum L. (Berberidaceae.)	Etoposide	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Podophyllum peltatum L. (Berberidaceae.)	Teniposid	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Triptery Giumwilfordii Hook F. (Celastraceae)	Triptolide	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Brucea antidysenterica J. F. Mill. (Simaroubaceae)	Bruceantina	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Rheum palmatum L. (Polygonaceae)	Emodin	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Artemisia annua L. (Asteraceae)	Artesunate	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Cephalothaxus harringtonia (Knight ex J. Forbes) K. Koch, *C. haianensis* H.L. Li *and C. sinensis* (Rehder & E.H. Wilson) H.L. Li (Taxacea)	Homoharrigtonine	Potent antitumor activity	Potent antitumor activity	(Tirado-Hurtado et al., 2018)
Combretum caffrum (Eckl. &Zeyh.) Kuntze (Combretaceae)	Phosphate 3 and AVE-8062 (derived from Combretastatin A4)	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Thapsia garganica L. (Apiaceae)	Tapsigargina	Potent antitumor activity		(Brandão et al., 2010)

			Potent antitumor activity	
B. sumatrana Roxbe *B. javanica* Merr**.** (Fabaceae)	Brusatol	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Maytenus serrata **(**Hochst. Ex A. Rich.) Wilczek (Celastraceae)	Maytansine	Potent antitumor activity	Potent antitumor activity	(Brandão et al., 2010)
Betulaalba L. (Betulaceae)	Betulynic acid	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Berberis amurensis Rupr. (Berberidaceae)	Berbamine	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Hvdrastis canadensis L., (Ranuncufaceae)	Berberine	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Colchicum autumnale L. (Colchiaceae) *Gloriosa superba* L. (Colchicaceae)	Colchicin	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Cucurbita maximum Duchesne and *Cucurbita moschata* Duchesne (Cucurbitaceae)	Cucurbitacin	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Wikstroemia indica (L.) C.A. Mey. (Thymelaeacea)	Daphnoretin	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Glycine max (L.) Merr. (Fabaceae)	Diadzein and Genistein	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Curcuma longa L. (Zingiberaceae)	Curcumin	Potent antitumor activity	Potent antitumor activity	(Tirado-Hurtado et al., 2018)
Ochrosia borbonica J.F. Gmel., *Excavatia coccinea* (Teijsm. & Binn.) Markgr, *Ochrosia elliptica* Labill. (Apocynaceae)	Elipticin	Potent antitumor activity against several neoplastic cell lines	Potent antitumor activity against several neoplastic cell lines	(Brandão et al., 2010)
Rheum rhabarbarum L. (Polygonaceae)	Emodine	Potent antitumor activity against lung, liver, ovarian and blood cancer	Potent antitumor activity against lung, liver, ovarian and blood cancer	(Nirmala et al., 2011)
Dysoxylum binectariferum (Roxb.) Hook. f. ex Bedd. (Meliaceae)	Flavopiridol	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Angelica sinensis (Oliv.) Diels (Apiaceae)	Indirubin	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Ipomoea batatas (L.) Lam. (Convolvulaceae)	4-Ipomeanol	Promising results for lung-specific cancer treatment	Promising results for lung-specific cancer treatment	(Nirmala et al., 2011)
Iris kumaoensis Wall. *(Iridaceae)*	Irisquinone	Efficient antitumor activity	Efficient antitumor activity	(Nirmala et al., 2011)
Erythroxylum pervillei Baill (Erythroxylaceae)	Pervilleinas A, B, C, and F	Efficient antitumor activity	Efficient antitumor activity	(Nirmala et al., 2011)

Mentha x balsamea Willd (Lamiaceae)	Peryl alcohol	Potent antitumor activity by inhibiting the growth of neoplastic cells	Potent antitumor activity by inhibiting the growth of neoplastic cells	(Nirmala et al., 2011)
Cenaurea schischkinii Tzvelev (Asteracee)	Schischkinnin	Moderate antitumor activity	–	(Nirmala et al., 2011)
Centaurea montana L. (Asteraceae)	Montamine	Moderate antitumor activity	–	(Nirmala et al., 2011)
Aglaia foveolata Panell (Meliaceae)	Silvestrol	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)
Aglaia foveolata Panell (Meliaceae)	Episilvestrol	Moderate antitumor activity	Moderate antitumor activity	(Nirmala et al., 2011)
Tripterygium wilfordii F. Hook (Celastraceae)	Triptolide	Potent antitumor activity	Potent antitumor activity	(Nirmala et al., 2011)

Source: Authors.

3.7 Effects already observed on the use of the substances found

Drugs, either of natural or synthetic origin, which are selected for a medical clinic, must fulfill some criteria as exhibiting a high beneficial effect with negligible side effects (Castro, 2002). Table 3 shows substances and their respective promising effects.

Table 3. Relationship between metabolites found in plants and their promising effects.

Substances	Effects
Biflorin	The metabolite Bioflorin a was tested in HL60 leukemic cells, and through the analyses the induction of cell differentiation was observed and, in melanoma cells B16F10, inhibition of tumor colonization in the lung, demonstrating an antimetastatic potential, increasing the survival of the animals. Besides not presenting mutagenicity being considered an effective and safe metabolite (Costa-Lotufo et al., 2010).
Pisosterol	Potent ability to inhibit tumor growth of Sarcoma 180 and also, a potent inducer of cell differentiation, leading hl-60 leukemic cells to monocytic differentiation. (Costa-Lotufo et al., 2010).
Ixabepilone	It was effective in the test of antitumor activity in the treatment of breast cancer (Barreiro & Bolzani, 2009).
Salvicin	Potent anticancer activity against three types of leukemia (Silva, 2003). Extensive anti-metastasis activity (Brandão et al., 2010).
β-lapachona	Potent antitumor effects against breast cancer, prostate cancer, lung cancer, pancreatic cancer and also in promyelocytic leukemic cells (Nirmala et al., 2011).
Vinblastine	Active in testicular cancer, acute lymphoblastic leukemia, Hodgkin lymphoma (Costa-Lotufo et al., 2010).
Vincristine	Presents activity against testicular cancer, Hodgkin lymphoma, acute lymphoblastic leukemia (Costa-Lotufo et al., 2010). Being used in combined therapies for the treatment of childhood leukemias and lymphomas, however, neurotoxicity is the main side effect observed (Brandão et al., 2010).
Vinorelbine	Presents activity against testicular cancer, Hodgkin lymphoma, acute lymphoblastic leukemia (Costa-Lotufo et al., 2010). For having an extensive spectrum of antitumor activities being active in breast cancer and lung

	carcinoma. This alkaloid when compared with other crease metabolites is more active and less neurotoxic (Brandão et al., 2010).
Vindesine	Active in testicular cancer, acute lymphoblastic leukemia, Hodgkin lymphoma (Costa-Lotufo et al, 2010). It presents activity against breast cancer, hematological malignancies, melanoma, lung adenocarcinoma, especially those resistant to vincristine (Brandão et al., 2010).
Camptothecin	It presented low solubility and severe toxicity and, for this reason, certain analogs were synthesized to overcome these disadvantages (Nirmala et al., 2011).
Etoposide	Active against lung cancer, soft tissue sarcomas, Kaposi, neuroblastoma and Hodking lymphomas (Brandão et al., 2010).
Teniposid	Its main use is in the treatment of childhood lymphomas, leukemia cancers in the central nervous system, acute lymphoblastic leukemia in children, in adults in cases of bladder cancer (Brandão et al., 2010).
Bruceantina	Important activities were observed in leukemia, lymphoma and myeloma cell lines. However, adverse effects such as hypotension, nausea and vomiting were observed, as well as moderate hematological toxicity, e.g., thrombocytopenia (Brandão et al., 2010).
Emodin	It has been observed that this metabolite can induce apoptosis in several human cancer cell lines such as lung, liver, ovarian and blood cells (Brandão et al., 2010).
Artesunate	Because it presents low toxicity, this is promising antileukemic chemotherapy (Brandão et al., 2010).
Homoharrigtonine	Actives against leukemia and breast cancer. (Tirado-Hurtado et al., 2018).
Tapsigargina (TG)	Apoptosis induction was observed in quiescent and proliferative prostate cancer cells, being a promising cytotoxic molecule (Brandão et al., 2010).
Maytansine	It has appreciable antimycotic activity in breast cancer (Brandão et al., 2010).
Betulynic acid	Its anticancer properties have been demonstrated against rectal colo pulmonary lung, colon, breast, prostate, hepatocellular, bladder, headache, stomach, pancreas, ovarian and cervical carcinoma, glioblastoma, chronic myeloid leukemia cells, and human melanoma (Tirado-Hurtado et al., 2018).
Berbamine	Causes apoptosis in myeloid leukemia tumor cells. (Nirmala et al., 2011).
Berberine	Efficacy against osteosarcoma, lung, liver, prostate, and breast cancer (Nirmala et al., 2011).
Colchicin	It acts as an antimycotic; Due to the severe toxic effects, certain derivatives of colchicine were synthesized, namely 3-dimethyl-colchicine, colchicine, thiocolchicocida, which showed improved activity against certain leukemic cells and solid tumors. Research is still conducted in the area of anticancer therapy (Nirmala, Samundeeswari &Deepa Sankar, 2011).
Cucurbitacin	Active in prostate cancer, breast cancer, and also head, neck, and nasopharynx carcinoma (Nirmala et al., 2011).
Daphnoretin	Prevents the development of Ehrlich Ascites carcinomas (Nirmala et al., 2011).
Diadzein	Action against cell proliferation in ovarian and breast cancer was observed, in addition to inhibition of chemically induced cancers in the blood, colon, stomach, bladder, lung and prostate (Nirmala et al., 2011).
Curcumin	It has an important antineoplastic effect on prostate, skin and breast tumors, in addition to activity in brain tumors, pancreas, lungs and leukemias (Tirado-Hurtado et al., 2018).
Elliptical	Particularly active in breast cancer (Brandão et al., 2010).

Emodin	Important activities such as antitumor effects on human cells in the lungs, liver, ovary and blood (Brandão et al., 2010).
Flavopiridol	Active in rectal cancer, non-small cell lung, renal cell carcinoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia and also solid tumors (Nirmala et al., 2011).
Indirubin	Potent antitumor activity for the treatment of chronic myeloid leukemia (Nirmala et al., 2011).
4-Ipomeanol	Showed promising results for specific lung cancer in preclinical studies with animal models. But unexpectedly, poor results were obtained in clinical trials (Nirmala et al., 2011).
Irisquinone	Efficient against tumors transplanted in rodents; it also acts as chemo sensitizing (Nirmala et al., 2011).
Pervilleinas A, B, C, and F	They act as good P glycoprotein inhibitors, which cause resistance to multiple drugs related to the low response to cancer therapy. Further research into clinical trials is still to be done (Nirmala et al., 2011).
Peryl alcohol	The effectiveness of a chemotherapeutic activity against human cancers, such as non-small cell lung cancer, prostate cancer, and colon cancer, is still being investigated. The combined therapies were used in the treatment of breast cancer cells (Nirmala et al., 2011).
Schischkinnin	Most of these compounds are found effective against colon cancer cell lines in vitro (Nirmala et al., 2011).
Montamine	Demonstrated an important potential in vitro anticancer against $_{CaCO2}$ colon cancer cells (Nirmala et al., 2011).
Silvestrol	They are effective against prostate, breast and lung cancer (Nirmala et al., 2011).
Episilvestrol	It is an epimer of silvestrol considered less effective as a cytotoxic agent when compared to the first (Nirmala et al., 2011).
Triptolide	Due to their severe toxicity and insolubility in water, new derivatives were synthesized, such as PG490-88 or F60008, which are soluble in water and proved to be very safe and effective (Nirmala et al., 2011).

Source: Authors.

3.8 Plant-derived anticancer (Vinca, Paclitaxel and Epotylona)

In the sphere of cancer, the elaborate complexes have been increasingly essential, since products of natural origin result in more than half of all molecules produced, whether natural or derivative (Leite, 2014).

Elements taken from natural products with anticancer action aim to interact with proteins and microtubules. In which the latter are long tube-shaped filaments, formed by amino acid macromolecules linked to each other, which are indispensable constituents of the cytoskeleton, is extremely important in cells that have defined nucleus. They are paramount for the functioning and shape of cells, assisting in the defined function. The procedure demands the dynamic balance between the order of the microtubules, in view of this imbalance-related disturbances cause the mitosis to stop, resulting in the death of the cell (Brandão et al., 2010).

The microtubules consist of a protein formed by two different subunits of α-tubulin and β-tubulin arranged and tuned. Its function in mitosis and cell division is the search for anticancer agents, which can be mentioned as the alkaloids of Vinca, taxonomy and colchicine (Brandão et al., 2010).

Vinca alkaloids influence macromolecule degradations into simpler molecules, causing them to bind to β-tubulins blocking the union of molecules for the formation of a polymer. Most of the substances from Vinca with mitosis blocking activity contain the structure without varied asymmetry and few changes, in which significant differences become both related to toxicity and in antitumor activities (Leite, 2014).

The mechanism of action in which vinblastine acts is by filament to β-tubulin units that do not have characteristic sites for alkaloids, performing a rapid and change in the bond, causing transformations in tubulin ordering and avoiding aggregation with identical molecules. The junction can also be performed directly with the microtubules by the positive terminal limit, without necessarily causing depolymerization and reversible myelosuppression (Brandão et al., 2010).

Clinically Vincristine is used in therapies stipulated for the treatment of cancer in which, the gathering of sick cells in the bone marrow occurs, obtaining the replacement of healthy cells in children and Hodgkin's disease. The main side effect of the drug is neurological toxicity, where the patient has several signs such as drowsiness, slow thoughts, changes in the Central Nervous System and others (Brandão et al., 2010).

In the experience of obtaining better results from *C. roseus*, the category went through several biotechnological methods related to its secondary metabolism, and besides that, other non-natural derivatives emerged as an option to modify molecules, improving their therapeutic activity and minimizing related adverse effects (Brandão et al., 2010).

As a result of one of the vinca's totally unnatural alkaloid derivatives, vinorelbine or nor-5'-anhydrovimblastin (Navelbine) has appeared, where it presents a® wide tumor inhibitor activity, actively acting on breast and non-small-cell lung cancer. Showing with more pharmacological activities and fewer adverse effects, providing a higher quality of life to the patient (Brandão et al., 2010).

The first representation of the class of taxanes to obtain permission by the Federal Administration of Food and Medicines (FDA) was Paclitaxel, which presented efficacy in several tumors in nanomolar richness, having as an example infiltrating breast cancer and malignant epithelial tumors of the ovary. In addition, it was the first medicine to prevent the degradation of macromolecules to small and simple molecules of globular proteins. Thus, research increases abruptly, with the purpose of verifying pharmacological groups and developing more effective drugs in cancer treatment (Leite, 2014).

With advanced studies and the success of paclitaxel, the research gained special attention in different groups. One of them was epothilones A and B that started from the perishing of cellulose by the microorganism *Sorangium cellulosum.* Many tests were performed and scientifically proven the antitumor action close to the activity present in paclitaxel, leaving cell replication to exist, establishing the properties of tubulin (Leite, 2014). And consequently, minimizing undesirable effects, and inhibiting glycoprotein-P13, a protein that develops drug resistance, with greater activity in relation to paclitaxel, due to its blocking of resistance to cells (Leite, 2014).

4. Conclusion

However, it can be concluded that neoplasms come from several genetic mutations. Currently, the different neoplasms cause fear to the population due to their high mortality rate. With this, the studies are increasingly present in the routine of researchers and scientists, causing them to seek new drugs for the cure of cancer, having as main objective the reduction of side effects, in addition not only to eliminate cancer cells but also to affect beneficial cells to the body.

Chemotherapy drugs used in the treatment of cancer, are antibiotics with anticlastic activity, these are of synthetic origin, however, there are several studies that prove antimicrobial and anticlastic activities in compounds found in plants.

There are few antineoplastic drugs of natural origin, on the other hand, Brazil has several biomes and plants with multiple chemical compounds of pharmacological interest. The discovery of compounds with antitumor properties such as alkaloids, flavonoids, among others and their respective pharmacological evidence exposes the vast field for scientific exploration of natural products and the opportunity to develop medicines of natural origin with higher quality than those developed synthetically.

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